Systemic mastocytosis with associated acute myelogenous leukemia

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Systemic mastocytosis (SM) is a condition associated with a clonal neoplastic proliferation of mast cells. Approximately 40% of patients with SM present with an associated clonal hematological non–mast cell lineage disorder. Patients presenting with SM–acute myeloid leukemia (AML) have the worst prognosis. We present a case of a 62-year-old woman who was diagnosed with SM-AML. After initial treatment with a standard regimen of cytosine arabinoside (Ara-C)/idarubicin, her bone marrow showed residual blasts. She was subsequently treated with a second induction regimen of clofarabine and high-dose Ara-C, which resulted in remission of AML, although a residual mast cell infiltrate persisted in her bone marrow. After consolidation therapy with clofarabine/Ara-C, the patient received a stem cell allograft. A follow-up bone marrow showed no residual blasts but persistent mast cells occupying about 5% of the marrow volume.

Mastocytosis is a clonal neoplastic proliferation of mast cells that accumulate in one or more organ systems. According to the latest classification from the World Health Organization, there are seven subtypes of mastocytosis (1). The second most common type of mastocytosis is known as systemic mastocytosis with an associated clonal hematologic non–mast cell lineage disorder (SM-AHNMD). These non–mast cell lineage disorders may include myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), acute myeloid leukemia (AML), chronic myelogenous leukemia, MDS/MPN, plasma cell myeloma, non-Hodgkin lymphoma, and unclassifiable myelogenous malignancy (2). An associated AML has the worst prognosis (3). We present a case of mastocytosis associated with an AML and discuss the pathology and treatment.

PATIENT DESCRIPTION

A 62-year-old white woman was noted to have a pancytopenia 3 years prior to admission. Her hematocrit was 30%, white blood cell count 3300 K/uL with 44% neutrophils, and platelet count 109,000 K/uL. Bone marrow biopsy revealed trilinear maturation without an abnormal infiltrate and normal cytogenetics and flow cytometry. Her spleen was enlarged, and the liver was infiltrated by adipose tissue. Her body mass index was 25.1 kg/m^2. She was believed to have steatohepatitis with pancytopenia secondary to hypersplenism.

Two years later, her pancytopenia and splenomegaly were unchanged. She now had fatigue, dyspnea, and fever (99°F) for 2 weeks. Her white blood cell count was 63,000/mm^3 with 38% circulating blasts, hematocrit 27%, and platelets 57,000/mm^3. A bone marrow biopsy showed 50% infiltration with mast cells and 50% myeloblasts, confirming the entity of SM-AHNMD *(Figure 1)*. Results of an AML fluorescent in situ hybridization panel and routine cytogenetics were negative. She had a *C-KIT* D816V mutation but no *JAK-2* mutation. Her serum tryptase level was 189 ng/mL (normal level, <11.4).

The patient was admitted to the hospital and underwent induction chemotherapy with cytosine arabinoside (Ara-C) (100 mg/m^2/day by continuous infusion for 7 days) and idarubicin (12 mg/m^2/day for 3 days). She was also started on dasatinib at 100 mg orally daily. Bone marrow biopsy 14 days after induction of treatment revealed persistent myeloblasts and mast cell infiltrate requiring a second course of therapy with 5 days of high-dose Ara-C (1 g/m^2/day) and clofarabine (40 mg/m^2/day). Because of the persistent mast cell infiltrate, dasatinib was discontinued. Her blood counts recovered on discharge, except for a platelet count of 40,000 K/uL. Her white blood cell count was 8,900 K/uL, and her hematocrit was 32.2%.

Repeat bone marrow biopsy showed no residual myeloblasts, with residual mast cells of 15%. Her tryptase level decreased to 77 ng/mL. She was readmitted 3 weeks later for consolidation chemotherapy with clofarabine/Ara-C. Four weeks later she had a stem cell allograft using an unrelated donor with a preparative regimen of busulfan and cyclophosphamide. Follow-up marrow revealed no evidence of AML, 5% residual mast cell infiltrate, and focal increased reticular fibrosis.

DISCUSSION

The diagnosis of SM-AHNMD may be difficult to establish, as the histologic and cytologic features of systemic mastocytosis

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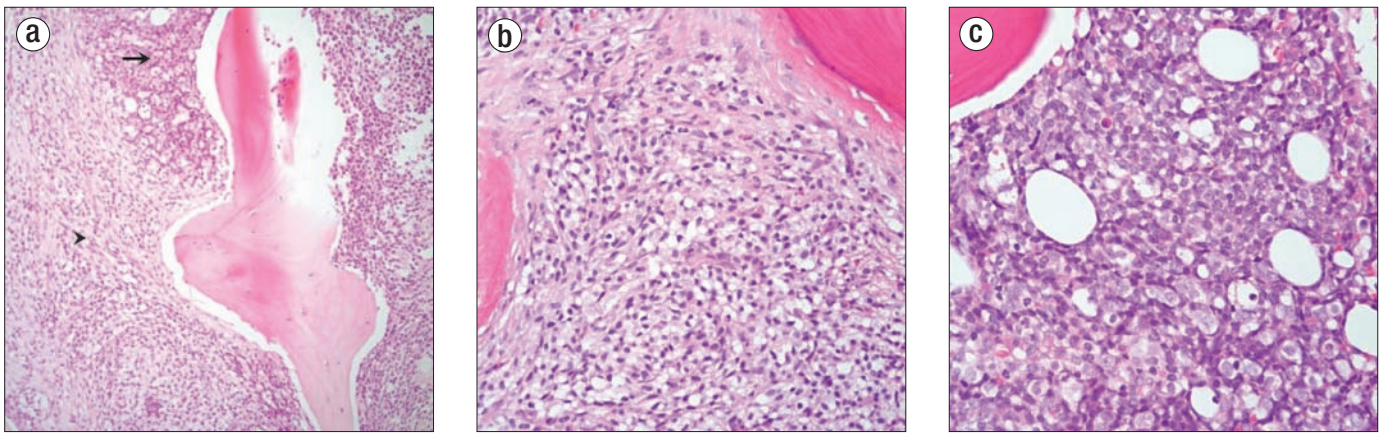

Figure 1. A bone marrow biopsy showing **(a)** a leukemic infiltrate (arrow) and mast cell infiltrate (arrowhead), hematoxylin and eosin (H&E) ×200; **(b)** a mast cell infiltrate, H&E ×400; and **(c)** a leukemic infiltrate, H&E ×500.

(SM) may be masked by the associated malignancy. The diagnosis can only be made when there is clear morphologic evidence of both SM with multifocal tissue infiltrates and an AHNMD, as in this case (4). Malignant mast cells may abnormally express CD2 and/or CD25, which may be detected by immunochemistry or flow cytometry. This is helpful in distinguishing neoplastic mast cells ($CD25^+$ and/or $CD2^+$) from reactive mast cells ($CD2^-$ and $CD25^-$). Activating c-kit mutations are considered the hallmark of neoplastic mast cells (5).

The pathogenesis of SM associated with AHNMD is unknown, and the non–mast cell lineage component might or might not show evidence of the same c-kit mutation seen in the neoplastic mast cells. When there is an associated myeloid neoplasm, there are two proposed theories for the pathogenesis. One theory involves an activating c-kit mutation that occurs with other genetic mutations and events in a myeloid stem cell (6, 7). The c-kit mutation could result in a proliferative advantage to the mutated stem cell and lead to mast cell differentiation and proliferation (8). Another possible mechanism is transformation of a subclone of the myeloid progenitor cells through an acquired c-kit mutation resulting in a coexisting mastocytosis (9). The association with c-kit mutations in SM associated with lymphoid neoplasms is even less apparent, as mutations have not been reported in these cases.

It is important to distinguish SM-AHNMD from other entities associated with mast cell differentiation. These include tryptase-positive AML, MDS with prominent involvement of the mast cell lineage, and systemic mastocytosis associated with the hypereosinophilic syndrome and myeloproliferative disorders associated with *PDGFRA* or *PDGFRB* fusion genes. None of the aforementioned entities would be classified as SM-AHNMD. Among patients with SM-AHNMD, those with SM-MPN have a significantly longer median survival than patients with SM-CMML (chronic myelomonocytic leukemia), SM-MDS, and SM-AML, which has the worst prognosis (3).

We initially treated our patient with a standard AML regimen of Ara-C/idarubicin, adding dasatinib, which has been reported to induce apoptosis of leukemia cells expressing c-KIT. The combination of drugs induced molecular remission in a similar patient reported by Ustun et al (10). Clofarabine was added along with a second course of Ara-C when persistent disease was found after the initial cycle of therapy. Phase II studies from M. D. Anderson Center as well as Baylor University Medical Center at Dallas showed that the combination of clofarabine and Ara-C is effective in both untreated and previously treated patients with AML and can serve as a bridge to transplantation in older patients with AML. Our patient did achieve a complete remission of AML with this regimen, albeit there was a persistent mast cell infiltrate. Clofarabine is an adenosine deaminase analog similar to fludarabine and cladribine. In fact, cladribine as a single agent is an effective drug to treat systemic mastocytosis, with all nine patients treated with this drug having a partial response, as reported by Hanneke at al (11). Finally, in our patient there was a further decrease in the mast cell infiltrate 4 weeks after transplant.

1. Swerdlow SH, Campo E, Harris NL, Jaffee ES, Pileri SA, Stein H, Thiele J, Vardiman JW. *WHO Classification of Tumors of Haematopoietic and Lymphoid Tissue.* Lyon, France: IARC, 2008.
2. Pullarkat VA, Bueso-Ramos C, Lai R, Kroft S, Wilson CS, Pullarkat ST, Bu X, Thein M, Lee M, Brynes RK. Systemic mastocytosis with associated clonal hematological non-mast-cell lineage disease: analysis of clinicopathologic features and activating c-kit mutations. *Am J Hematol* 2003;73(1):12–17.
3. Pardanani A, Lim KH, Lasho TL, Finke C, McClure RF, Li CY, Tefferi A. Prognostically relevant breakdown of 123 patients with systemic mastocytosis associated with other myeloid malignancies. *Blood* 2009;114(18):3769–3772.
4. Stoecker MM, Wang E. Systemic mastocytosis with associated clonal hematologic nonmast cell lineage disease: a clinicopathologic review. *Arch Pathol Lab Med* 2012;136(7):832–838.
5. Féger F, Ribadeau Dumas A, Leriche L, Valent P, Arock M. Kit and c-kit mutations in mastocytosis: a short overview with special reference to novel molecular and diagnostic concepts. *Int Arch Allergy Immunol* 2002;127(2):110–114.
6. Bonnet D, Dick JE. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. *Nat Med* 1997;3(7):730–737.

7. Jordan CT. Unique molecular and cellular features of acute myelogenous leukemia stem cells. *Leukemia* 2002;16(4):559–562.
8. Horny HP, Sotlar K, Sperr WR, Valent P. Systemic mastocytosis with associated clonal haematological non-mast cell lineage diseases: a histopathological challenge. *J Clin Pathol* 2004;57(6):604–608.
9. Wang SA, Hutchinson L, Tang G, Chen SS, Miron PM, Huh YO, Jones DM, Bueso-Ramos C, Verstovsek S, Medeiros LJ, Miranda RN. Systemic mastocytosis with associated clonal hematological non-mast cell lineage disease: clinical significance and comparison of chromosomal abnormalities in SM and AHNMD components. *Am J Hematol* 2013;88(3):219–224.
10. Ustun C, Corless CL, Savage N, Fiskus W, Manaloor E, Heinrich MC, Lewis G, Ramalingam P, Kepten I, Jillella A, Bhalla K. Chemotherapy and dasatinib induce long-term hematologic and molecular remission in systemic mastocytosis with acute myeloid leukemia with KIT D816V. *Leuk Res* 2009;33(5):735–741.
11. Kluin-Nelemans HC, Oldhoff JM, Van Doormaal JJ, Van't Wout JW, Verhoef G, Gerrits WB, van Dobbenburgh OA, Pasmans SG, Fijnheer R. Cladribine therapy for systemic mastocytosis. *Blood* 2003;102(13):4270–4276.